IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of: Activus Pharma Co., Ltd.

Application No.: 10/565,828

Filling Date: 01/25/2006

Art Unit: 1612 Examiner: SIMMONS, CHRIS E

Title: THERAPEUTIC AGENT FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND METHOD FOR TREATING CHRONIC OBSTRUCTIVE PULMONARY DISEASE USING THE SAME

DECLARATION

Dear Sir:

I, Yasuo AOKI, residing in Yotsukaido-shi, Japan, declare and state that:

1. I graduated with a Ph.D. from Toho University in August 15, 2001. Since April 1985, I had been employed by Dainippon Ink and Chemicals, Inc., and at the time of the invention, I was engaged in research and development.

2. I am one of the inventors of the invention as claimed in the above-referenced application, and accordingly, I am familiar with the specification and claims which compose the application.

3. I am aware of the Office Action of March 30, 2010, issued on the above-referenced application.

4. In order to supplement the declaration as filed on July 30, 2008, I conducted an additional experiment for the purpose of demonstrating that unexpected effects can be obtained by the claimed subject-matter, and the experimental procedures and obtained data are presented below.

Experiment 1

In "Experiment 2" in the Declaration as filed on July 30, 2008, the administration doses between TA-270 and theophylline were different. Although we believe that the unexpected effects of TA-270 were shown sufficiently in Experiment 2,

we would like to present additional experiment showing the effects on COPD in the same dose between TA-270 and theophylline. In this experiment, TA-270 and theophylline were intra-tracheally administered to COPD mice induced by lipopolysaccharide (LPS) and evaluated on its efficacy and prolonged effect. This COPD model was reported in Am J Physiol Lung Cell Mol Physiol (295: L1–L15, 2008). Materials and procedures thereof are summarized below.

MATERIALS AND METHODS

[Animals]

Male, 7-week-old, Balb/c mice weighing around 20 g were purchased from Japan SLC (Hamamatsu, Japan). The animals were housed in a temperature-controlled environment with free access to standard rodent chow and water. All of the experimental procedures were approved by the Experimental Animal Research Committee at Kobe Pharmaceutical University.

[Reagents]

LPS (Escherichia coli 055:B5) and Bovine serum albumin were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). Theophylline was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan).

The vehicle for intra-tracheal administration was used 0.1w/v% BSA–saline solution. 10 μg/mL 0.1w/v% BSA–saline solutions of TA-270 and theophylline were prepared using agate mortar as a test drug solution.

0.5 mg/mL of LPS solution was prepared using saline

[Study design]

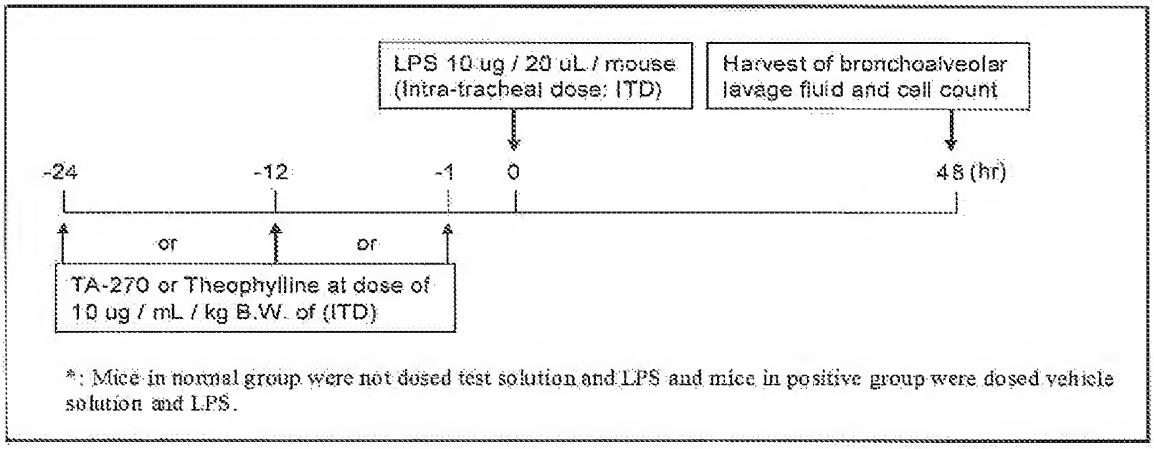
The protocol followed in this study is summarized in FIG. 1 below. LPS (10 μL•animal-1) was intra-tracheally administered under consciousness. Subsequently, BALF was harvested from all mice at 48 hour after intra-tracheal dosing of LPS. Total cells and differential cells counts including macrophages, lymphocyte, neutrophils and eosinophils in BALF were performed.

To evaluate the effect of TA-270 (compound No. 551) (10 μg•kg-1) and

theophylline (10 μg•kg-1) were intra-tracheally administered 1, 12 or 24 hour before the intra-tracheal instillations of LPS. As a normal group, test compounds and LPS were not administered, and as a positive group, vehicle solution and LPS were administered.

The results are shown in FIG. 2.

FIG. 1 COPD model induced by lipopolysaccharide (LPS)



[Result]

Total cell, macrophages, lymphocyte and neutrophil counts in BALF of the positive group were significantly increased through the intra-tracheal dose (ITD) of LPS comparing to the normal group. Eosinophils did not detected in any groups including to normal, positive and test compound groups.

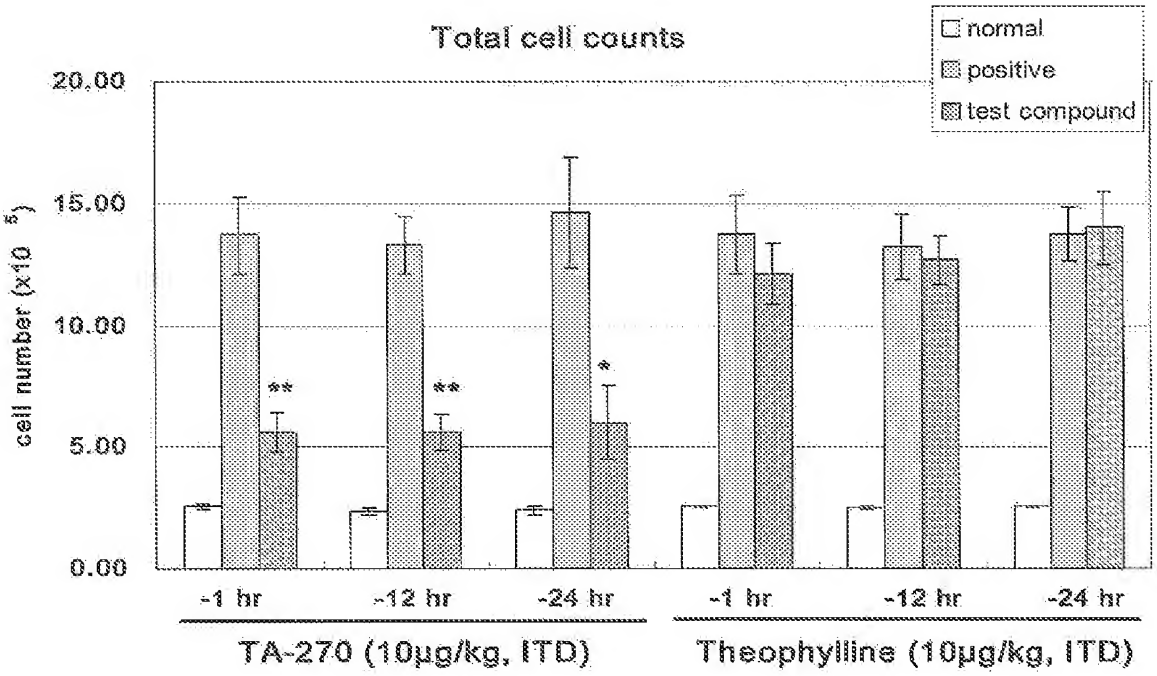
TA-270 showed the significant inhibitory effects on the infiltration of inflammatory cells into airway by intra-tracheal dose at dose of 10 μg / kg. Additionally, TA-270 showed the significant effect by intra-tracheal dose at 24 hour prior to administration of LPS and this long-acting effects meant the possibility that TA-270 was effective in an inhalation dose once a day in COPD patients. These effects were not thought to be related to allergic reaction through eosinophils because eosinophils could not detect in this COPD model. On the other hand, theophylline did not show any inhibitory effects at similar dose of TA-270 in any dose timings.

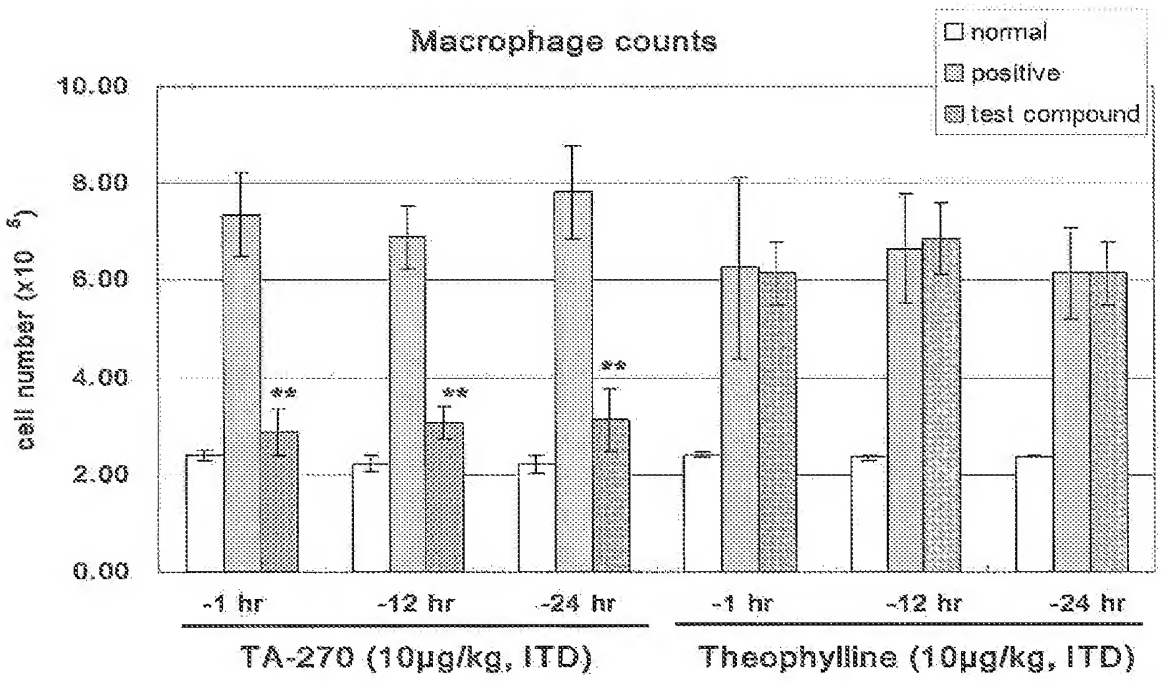
Therefore, as shown in "Experiment 2" of the declaration as filed on July 30, 2008 and this "Experiment 1", TA-270 has the unexpected and superior effects than existing medicine for COPD, theophylline, in two COPD animal models. TA-270

improved the residual volume, had stronger inhibitory effect on the infiltration of inflammatory cells than theophylline and showed the long-acting effects in COPD model.

From these results, we concluded that TA-270 has the unexpected, very useful and effective effects for COPD patients.

FIG. 2 Effect of TA-270 and theophylline on the increase in cell counts in the airway of COPD mice induced by LPS




Macrophage counts
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positive
test compound
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8.00
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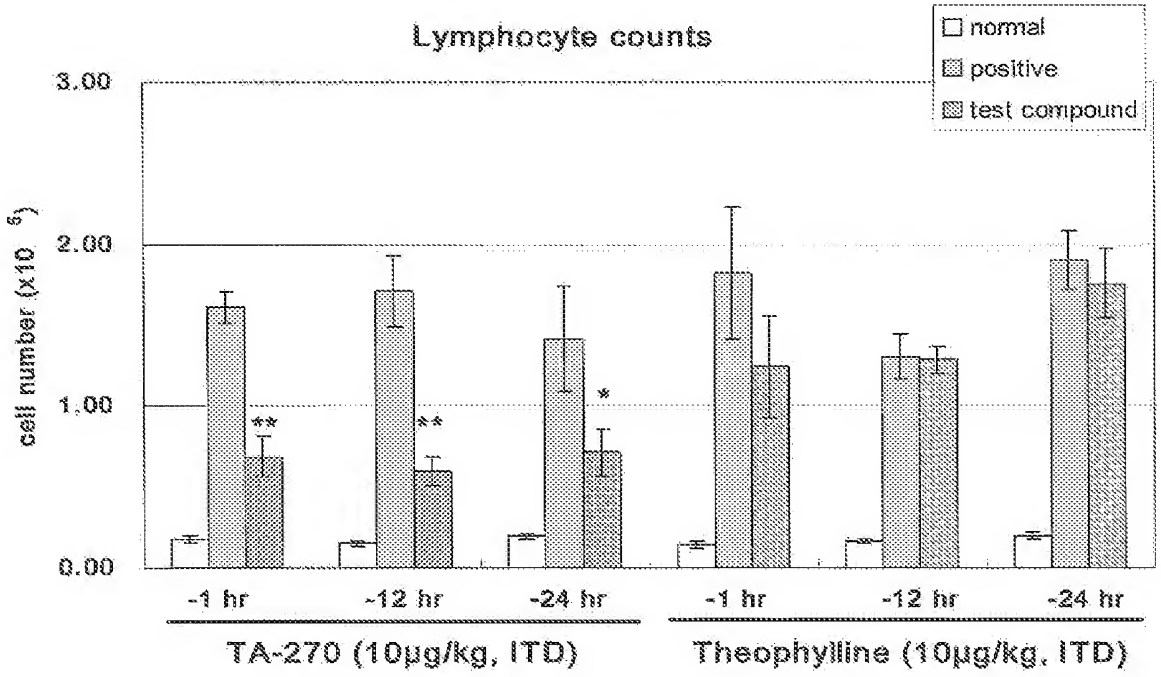
-1 hr
-12 hr
-24 hr
TA-270 (10μg/kg, ITD)
Theophylline (10μg/kg, ITD)


Lymphocyte counts
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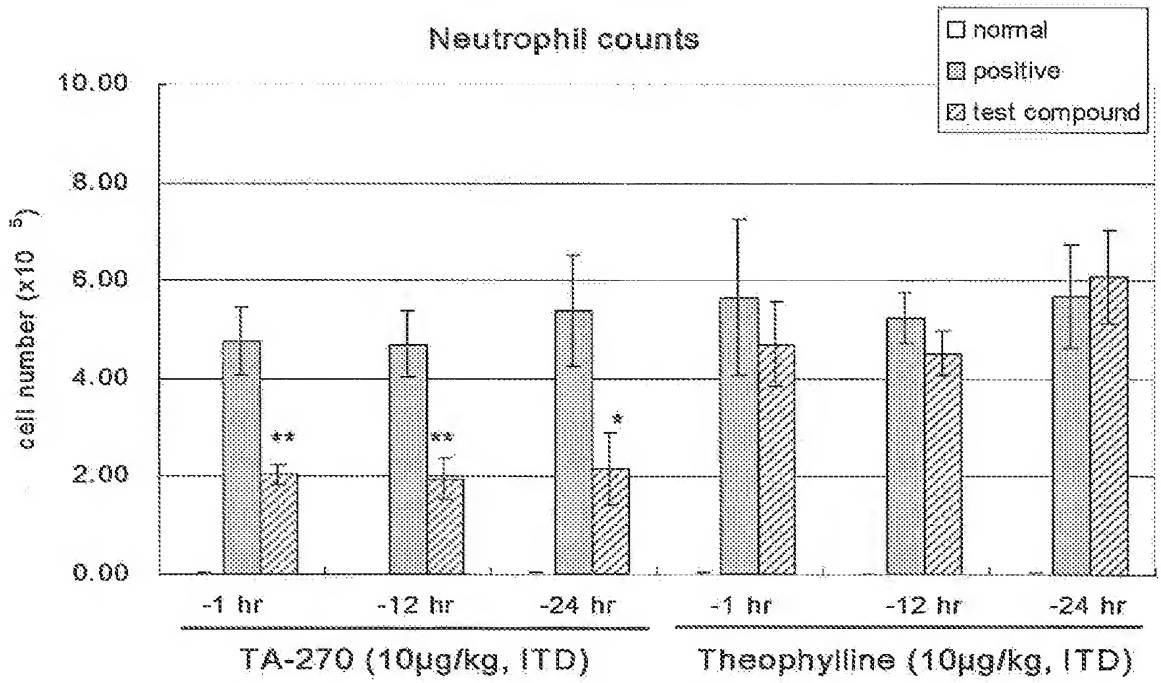
-1 hr
-12 hr
-24 hr
TA-270 (10μg/kg, ITD)
Theophylline (10μg/kg, ITD)



I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: September 15, 2010

Yasuo AOKI